



## Early View

Research letter

### **Jugular venous ultrasound predicts outcomes in pulmonary hypertension outpatients**

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## **Jugular venous ultrasound predicts outcomes in pulmonary hypertension outpatients**

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Take home message: Jugular venous pressure estimated using a handheld ultrasound was able to predict clinical worsening in pulmonary hypertension outpatients, even after adjusting for REVEAL risk score.

Assessment of jugular venous pressure (JVP) is a classic physical exam maneuver that serves as an estimate of right atrial pressure (RAP). Although JVP was rated by experts as the most important physical exam finding to monitor response to therapy in pulmonary hypertension (PH) patients[1], it has been understudied in PH. Since RAP is an accurate predictor of outcome in PH[2, 3], determining whether clinically assessed JVP (as a non-invasive surrogate for RAP) also predicts outcomes is an important, unanswered question. Since JVP can be difficult to measure on physical exam due to obesity and challenges distinguishing between carotid and jugular pulsations, ultrasound measures of JVP have been developed[4, 5]. We hypothesized that: 1) JVP measurement could be more reliably obtained by ultrasound (JVP-US) than JVP by physical exam (JVP-exam); 2) JVP-US would correlate with same-day B-type natriuretic peptide (BNP), another non-invasive surrogate of right heart function; and 3) JVP-US would predict time to clinical worsening (TTCW).

## Methods

This was a prospective, observational study at a United States Pulmonary Hypertension Association-accredited Comprehensive Care Center enrolling patients from July 2016 to April 2018, with follow-up ending April 2021. Consecutive patients from any World Symposium on PH (WSPH) subgroup[6] were eligible for inclusion. Informed consent was obtained from each patient prior to enrollment (IRB #9403, [clinicaltrials.gov NCT02873039](https://clinicaltrials.gov/ct2/show/study/NCT02873039)).

## **Clinical assessments**

The REVEAL 2.0 risk score[2], a multi-parameter risk prediction score was calculated using the most recent data from the medical record. The research team was blinded to patient's clinical status and BNP, and the treating physician was blinded to the results of the ultrasound measurement. A physical exam estimate of JVP ("JVP-exam") was performed by the treating physician by adding 5 cm H<sub>2</sub>O to the measured vertical height of the right internal jugular vein (IJV) V-wave above the sternal angle with the patient seated at a 45-degree angle. A handheld ultrasound (General Electric Vscan) was used to estimate JVP in the right IJV[4] with the patient in the same position. The probe was placed in a horizontal position in the anterior triangle of the neck and then rotated 90 degrees to obtain a longitudinal view of the JV. The vertical height of the IJV tapering above the sternal angle clavicle plus 5 cm H<sub>2</sub>O was used to estimate JVP ("JVP-US", Figure 1A). JVP measurements were taken at end-expiration.

## **Statistical analysis**

Baseline descriptive statistics were calculated and reported as mean  $\pm$  SD or percentages. Bland-Altman analysis was conducted to compare JVP-exam to JVP-US. Pearson correlation coefficients were calculated for both JVP-exam and JVP-US in relation to log-transformed BNP. Participants were followed prospectively for their first clinical worsening event (first occurrence of death, lung transplantation, PH-related hospitalization, or worsening functional class (FC) with addition of PH-specific medication[9]). Cox regression analysis was conducted to assess the relationship between JVP-exam and JVP-US and time to clinical worsening (TTCW), with adjustment for REVEAL 2.0 risk score. There was no significant

collinearity between JVP measurements and REVEAL 2.0 risk score, based on a variable inflation factor <10.

## Results

### **Baseline characteristics and JVP measurements**

Ninety PH patients were included, with the majority having pulmonary arterial or chronic thromboembolic PH (61% and 13%, respectively); sixty percent of patients were on PH-specific medications at study enrollment. The majority were FC II (55%) or III (38%) and the average REVEAL 2.0 risk score was  $7 \pm 3$ ; the median number of parameters available for each patient to calculate the REVEAL 2.0 score was 11.5, out of a possible 13 variables in the calculator. Full baseline characteristics of this cohort have been previously described[10].

JVP by exam was feasible in only 60% of patients. In contrast, JVP-US was measurable in 88% of patients ( $p < 0.0001$  compared to JVP-exam) in a median time of 1 minute (IQR: 1, 2 minutes). The average difference between JVP-exam and JVP-US was  $-0.5$  cmH<sub>2</sub>O (SD 1.4, 95% limits of agreement  $-3.3$  to  $2.2$ ). JVP-exam moderately correlated to logBNP ( $r = 0.60$ ,  $p < 0.0001$ ,  $n = 48$ ), although JVP-US only weakly correlated with logBNP ( $r = 0.39$ ,  $p = 0.001$ ,  $n = 69$ ).

### **Association of JVP assessments to clinical outcomes**

Forty-nine participants experienced at least one clinical worsening event (death=12, transplant=2, hospitalization=26, worsened FC with medication added=9) for a median at-risk follow-up of 2 years (IQR 1, 3). JVP-exam (HR 1.12, 95% CI 1.01-1.26,  $p = 0.03$ ) and JVP-US (HR 1.18, 95% CI 1.05-1.32,  $p = 0.004$ ) were both associated with TTCW. When adjusted for REVEAL 2.0 risk score, JVP-exam was no longer associated with TTCW (HR 1.09, 95% CI 0.97-1.23,  $p = 0.13$ , Figure 1C); however, JVP-US was independently associated with TTCW after adjustment

for REVEAL 2.0 risk score (HR 1.13, 95% CI 1.00-1.27,  $p=0.04$ , Figure 1D). In a sensitivity analysis restricted to WSPH group 1 and 4 patients, the results were similar (JVP-exam, after adjusting for REVEAL 2.0: HR 1.11, 95% CI 0.97-1.27,  $p=0.12$  and JVP-US, after adjusting for REVEAL 2.0: HR 1.18, 95% CI 1.02-1.36,  $p=0.02$ ).

## Discussion

In this prospective, observational study, we found that ultrasound measures of JVP were quick and highly feasible in the outpatient setting, and were independently associated with clinically important outcomes. To our knowledge, this is the first study to investigate the association of JVP (either by physical exam or ultrasound) with prognosis in PH patients. One prior study found that elevated JVP on physical exam had a moderate sensitivity for the diagnosis of PH[11] but that JVP-exam underestimates invasively measured RAP. This has also been demonstrated for JVP-US in non-PH populations[5, 12], with underestimation of RAP by 0.5-5 cmH<sub>2</sub>O. Interestingly, we found that JVP-US tended to be higher than JVP-exam.

Although the prospective design and the standardized protocols for measuring JVP-US and collecting clinical worsening events are strengths of our study, there are limitations that should be acknowledged. First, we did not have contemporaneous invasive measures of RAP, although this does not invalidate the importance of JVP-US in non-invasively predicting prognosis. Second, due the pragmatic nature of study, we included PH patients from all WSPH subgroups, although some outcomes (addition of PH meds, lung transplant) may not be relevant to those with non-group 1 PH (e.g. left-heart disease-PH). However, in a sensitivity analysis restricted to group 1 and 4 PH patients, JVP-US remained a significant independent predictor of TTCW. We chose to use the contemporary REVEAL 2.0 risk score since this is most

widely used in practice; however, when using the original REVEAL score for adjustment, which has been validated in non-WSPH group 1 PH[8], the results were unchanged (data not shown).

In conclusion, a simple, quick, and feasible ultrasound measure of JVP accurately predicted clinically relevant events in a broad group of PH patients independently of a robust predictor such as REVEAL risk score. If this is confirmed in other cohorts, JVP-US could be incorporated into outpatient PH practice.

## References

1. Borrie AE, Ostrow DN, Levy RD, Swiston JR. Assessing response to therapy in idiopathic pulmonary arterial hypertension: a consensus survey of Canadian pulmonary hypertension physicians. *Can Respir J* 2011; 18(4): 230-234.
2. Benza RL, Gomberg-Maitland M, Elliott CG, Farber HW, Foreman AJ, Frost AE, McGoon MD, Pasta DJ, Selej M, Burger CD, Frantz RP. Predicting Survival in Patients With Pulmonary Arterial Hypertension: The REVEAL Risk Score Calculator 2.0 and Comparison With ESC/ERS-Based Risk Assessment Strategies. *Chest* 2019; 156(2): 323-337.
3. Boucly A, Weatherald J, Savale L, Jais X, Cottin V, Prevot G, Picard F, de Groote P, Jevnikar M, Bergot E, Chaouat A, Chabanne C, Bourdin A, Parent F, Montani D, Simonneau G, Humbert M, Sitbon O. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur Respir J* 2017; 50(2).
4. Lipton B. Estimation of central venous pressure by ultrasound of the internal jugular vein. *Am J Emerg Med* 2000; 18(4): 432-434.
5. Deol GR, Collett N, Ashby A, Schmidt GA. Ultrasound accurately reflects the jugular venous examination but underestimates central venous pressure. *Chest* 2011; 139(1): 95-100.
6. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2019; 53(1).
7. Benza RL, Gomberg-Maitland M, Miller DP, Frost A, Frantz RP, Foreman AJ, Badesch DB, McGoon MD. The REVEAL Registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. *Chest* 2012; 141(2): 354-362.
8. Cogswell R, McGlothlin D, Kobashigawa E, Shaw R, De Marco T. Performance of the REVEAL model in WHO Group 2 to 5 pulmonary hypertension: application beyond pulmonary arterial hypertension. *J Heart Lung Transplant* 2013; 32(3): 293-298.
9. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galie N, Ghofrani HA, Jansa P, Jing ZC, Le Brun FO, Mehta S, Mittelholzer CM, Perchenet L, Sastry BK, Sitbon O, Souza R, Torbicki A, Zeng X, Rubin LJ, Simonneau G. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med* 2013; 369(9): 809-818.
10. Samant S, Tran HV, Uddo RB, deBoisblanc BP, Saketkoo LA, Saito S, Helmcke FR, Lammi MR. Use of Handheld Ultrasound to Estimate Right Atrial Pressure in a Pulmonary Hypertension Clinic. *Ann Am Thorac Soc* 2021.
11. Braganza M, Shaw J, Solverson K, Vis D, Janovcik J, Varughese RA, Thakrar MV, Hirani N, Helmersen D, Weatherald J. A Prospective Evaluation of the Diagnostic Accuracy of the Physical Examination for Pulmonary Hypertension. *Chest* 2019; 155(5): 982-990.
12. Kerleroux B, Pasco J, Dupuis M, Eustache M, Lemrabott A, Jouzel C, Albert C, Janot K, Morel B, Pruna A. Ultrasonographic assessment of the internal jugular vein for the estimation of central venous pressure in hemodialysis patients: A preliminary study. *J Clin Ultrasound* 2018; 46(4): 253-258.



## Figure Legends

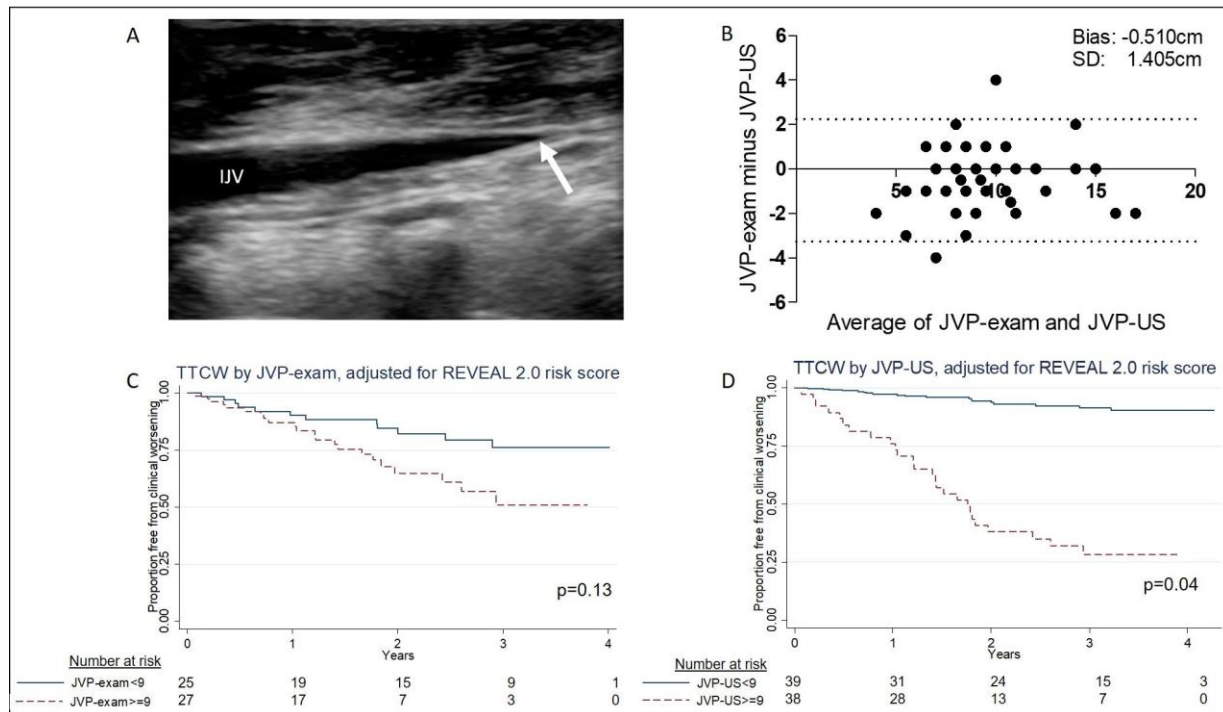


Figure 1: (A) Ultrasound image of the internal jugular vein (IJV) in the longitudinal view. The point of tapering (arrow) was determined and jugular venous pressure was derived as outlined in the Methods. (B) Bland-Altman plot showing the agreement between jugular venous pressure (JVP) by physical exam and ultrasound (US) [n=50 patients with both JVP-exam and JVP-US possible (some data points are superimposed)]. Dotted lines are the 95% limits of agreement. Kaplan-Meier curves for time to clinical worsening (TTCW) by median jugular venous pressure (JVP) by physical exam (C) and by ultrasound (D), both adjusted for REVEAL 2.0 risk score.